

# Ionic Liquid as a Suitable Phase for Multistep Parallel Synthesis of an Array of Isoxazolines

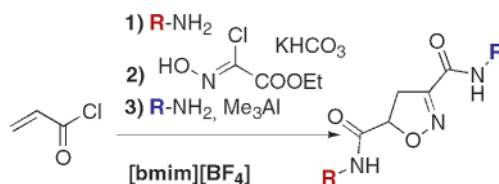
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Received July 25, 2003

## ABSTRACT



A parallel array of isoxazoline diamides was prepared using an ionic liquid [bmim][BF<sub>4</sub>] as the phase where a three-step procedure (Schotten–Baumann, 1,3-dipolar cycloaddition, ester amidation with Me<sub>3</sub>Al) was carried out. At the end, selective extraction of the final products with diethyl ether allowed simple isolation of the 16 components of the array (Syncore technology).

Ionic liquids are generally salts of quaternary ammonium species with poorly coordinating ions, liquids at temperature lower than 100 °C. The possibility of recycling them and the low vapor frame ensures their use in environmentally friendly technologies.<sup>1</sup> They have recently attracted considerable interest as solvents for a large series of organic transformations because they are immiscible with many organic solvents.<sup>2</sup>

(1) Chauvin, Y.; Olivier, H. *ChemTech* **1995**, 25, 26. Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, 68, 351. Olivier, H. *J. Mol. Catal. A: Chem.* **1999**, 146, 285. Welton, T. *Chem. Rev.* **1999**, 99, 2071. Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, 39, 3772. Zhao, H.; Malhotra, S. V. *Aldrichimica Acta* **2002**, 35, 75. Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, 102, 3667. Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, 182–183, 419. Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, 74, 157. Davis, J. H., Jr.; Fox, P. A. *Chem. Commun.* **2003**, 1209. *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2003.

(2) Some recent applications of ionic liquids in organic synthesis: Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, 1, 997. Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, 3, 233. Ren, R. X.; Wu, J. X. *Org. Lett.* **2001**, 3, 3727. Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett.* **2001**, 3, 1061. Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett.* **2001**, 3, 3785. Kabalka, G. W.; Dong, G.; Venkataiah, B. *Org. Lett.* **2003**, 5, 893. Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Tetrahedron* **2003**, 2253. Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Venkat Narsaiah, A. *Tetrahedron Lett.* **2003**, 44, 1047. Calò, V.; Scordari, F.; Nacci, A.; Schingaro, E.; D'Accolti, L.; Monopoli, A. *J. Org. Chem.* **2003**, 68, 4406.

The possibility to use ionic liquids as polar media to carry out organic reactions having polar transition states and to separate the organic products into an immiscible solvent targets them as potential candidates for the preparation of parallel arrays of compounds.

Although the beneficial effect of ionic liquid in a Suzuki–Miyura cross-coupling on solid phase has been previously reported,<sup>3</sup> we are unaware of previous publications describing the use of ionic liquids as medium for parallel multistep synthesis.<sup>4</sup>

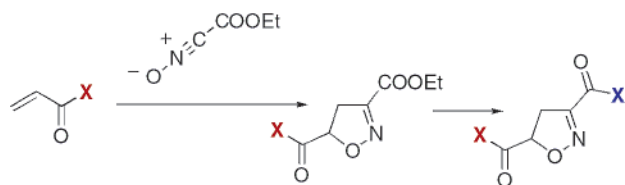
We recently discovered that cycloaddition of carbethoxylformonitrile oxide (CEFNO) with different alkenes is made easier in [bmim][BF<sub>4</sub>] or [bmim][PF<sub>6</sub>].<sup>5</sup> Using an acrylic derivative as the alkene, it is possible to obtain isoxazoline dicarboxylates, small rigid scaffolds with two groups suitable for further elaboration.

(3) Ravell, J. D.; Ganesan, A. *Org Lett.* **2002**, 4, 3071.

(4) Multicomponent reactions have been performed in ionic liquids: Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, 42, 5917. Fraga-Dubruel, J.; Bazureau, J. P. *Tetrahedron* **2003**, 59, 6121. Yadav, J. S.; Reddy, B. V. S.; Saritha Raj, K.; Prasad, A. R. *Tetrahedron* **2003**, 59, 1805. The use of a modified ionic liquid as support for organic synthesis also has been described: Fraga-Dubruel, J.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, 42, 6097.

(5) Conti, D.; Rodriquez, M.; Segà, A.; Taddei, M. *Tetrahedron Lett.* **2003**, 44, 5327.

Scheme 1



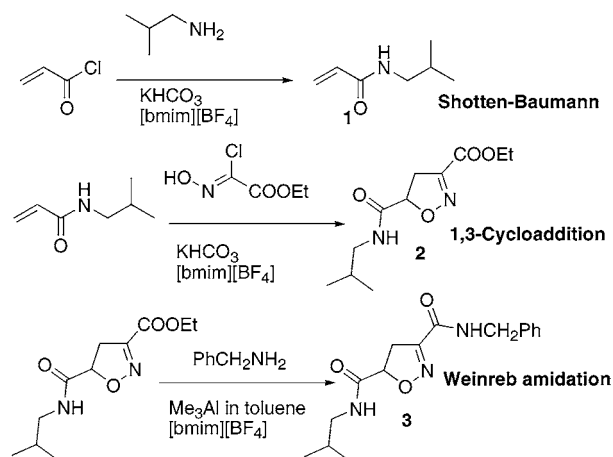
We focused our attention on this reaction to verify the potential of ionic liquids as medium for a multistep parallel synthesis of an array of differently substituted isoxazoline diamides. We wanted to verify whether it was possible to carry out a multistep procedure performed in a single reactor using the ionic liquid as the common phase. Selective extraction with an organic solvent immiscible with the ionic liquid phase would lead to the final pure compound.

As the first step, we investigated whether the single transformations could be carried out in ionic liquids. The Schotten–Baumann reaction of acryloyl chloride with isobutylamine worked well in [bmim][BF<sub>4</sub>]<sup>6</sup> in the presence of KHCO<sub>3</sub> as the base. The product was selectively extracted in diethyl ether and fully characterized. The yield of the isolated isobutylacrylamide **1** was 98%.<sup>7</sup> Cycloaddition with CEFNO was carried out adding ethylchlorooximido acetate<sup>8</sup> to a mixture of acrylamide **1** and KHCO<sub>3</sub> in [bmim][BF<sub>4</sub>] at room temperature for 12 h.<sup>9</sup> Selective extraction with ether gave isoxazoline **2** in 67% yield. Finally we looked for a procedure to transform esters into amides that could be carried out in ionic liquids. One potentially useful procedure is the MW-assisted transformation of esters into amide in the presence of *t*-BuOK,<sup>10</sup> which in our conditions gave unsatisfactory results.

Other attempts to carry out this reaction by heating the ester in ionic liquids in the presence of different activating agents were unsuccessful. We turned our attention to the Weinreb procedure that uses an aluminum amide prepared using Me<sub>3</sub>Al in organic solvent.<sup>11</sup> We were pleased to discover that this reaction worked very well by dissolving the ester and the amine (benzylamine) in [bmim][BF<sub>4</sub>], adding 4 equiv of a solution of Me<sub>3</sub>Al in toluene, and heating for 3 h. At the end, addition of an HCl aqueous solution followed by selective extraction with ether gave the diamide **3** in 79% yield (Scheme 2).

The same sequence of reactions was carried out using [bmim][BF<sub>4</sub>] as the common phase without isolation of the

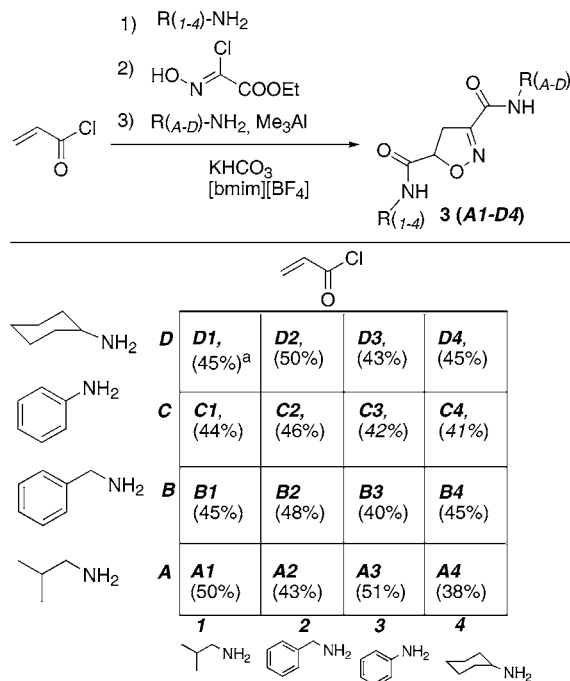
Scheme 2



single intermediates. Extraction with diethyl ether gave compound **3** in 43% overall yield pure by <sup>1</sup>H and <sup>13</sup>C NMR analysis (see Supporting Information).

We designed a strategy for the preparation of an array of disubstituted isoxazoline diamides (Scheme 3) using a

Scheme 3



<sup>a</sup> Yields of isolated products are in parentheses.

parallel synthesizer apparatus (Syncore from Büchi), which is particularly suitable for carrying out multistep reactions in ionic liquid phase. The 16 tubes were charged with 56 mg (0.62 mmol) of acryloyl chloride, 0.80 g of [bmim][BF<sub>4</sub>], and 62 mg of KHCO<sub>3</sub> each. Four different amines were added in the four columns of the plate (0.62 mmol), and the

(6) Prepared following: Dupont, J.; Consorti, C. S.; Suarez, P. A. Z.; de Souza, R. F. *Org. Synth.* **2002**, *79*, 236.

(7) Although trivial, no example of a Schotten–Baumann-like procedure in ionic liquids has been reported previously.

(8) **Warning:** while working with ethylchlorooximido acetate, one of us experienced a strong allergic erythema. The use of this reagent must be strictly controlled.

(9) Kozikowski, A. P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366. Abbott, S. D.; Lane-Bell, P.; Sidhu, K. P. S.; Vederas, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6513.

(10) Varma, R. J.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177. Perreux, L.; Loupy, A.; Delmotte, M. *Tetrahedron* **2003**, *59*, 2185.

(11) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

system was stirred at room temperature for 6 h. Ethylchloroimidate<sup>8</sup> (141 mg) was added in all tubes, followed by an additional 90 mg of KHCO<sub>3</sub>, and the system was stirred at 40 °C for 12 h. The same four amines (1.2 mmol) were added in the four rows of the system, followed by Me<sub>3</sub>Al (2.4 mL of a 1 M solution in toluene) in all of the tubes (under nitrogen).<sup>12</sup> The system was stirred at 70 °C for 12 h and then cooled, and a solution of HCl 2 N (600 μL) was added in each tube. The system was stirred for an additional 30 min.

Addition of ether (5 mL) in each tube followed by stirring for 1 h and separation of the ethereal layer<sup>13</sup> gave an array of 16 isoxazoline amides.<sup>14</sup> The composition of the array is reported in Scheme 3. In 14 cases the products were pure by <sup>1</sup>HNMR analysis (200 MHz). Two isoxazoline diamides (**3C1** and **3C4**) needed an additional purification by a short path chromatography.

With this experiment we have demonstrated that it is possible to carry out parallel multistep syntheses in an ionic

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(12) We decided to use the same amines in order to obtain the largest diversity with the lowest number of compounds. Other not-hindered amines can be equally used.

liquid with separation of the final low-polar products from polar byproducts and/or polar reagents by selective extraction in organic solvents. Work is in progress to examine the influence of ionic liquids on a variety of other multistep transformations.

**Acknowledgment.** The work was financially supported by MIUR (Rome) as a project within PRIN-2002. Nikem Research srl (Milan) is also acknowledged for financial support.

**Supporting Information Available:** Spectra of compounds **3(A1–D4)**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL035399L

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(13) The steps of addition and extraction were repeated three times, and the ethereal layers collected.

(14) Recycling of [bmim][BF<sub>4</sub>] was carried out as follows. The 16 collected ionic liquid phases were dissolved in water (200 mL) and washed several times with diethyl ether. The aqueous phase was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> (50 mL each), the organic phase collected and dried over anhydrous MgSO<sub>4</sub>, and the solvent was evaporated to give [bmim]-[BF<sub>4</sub>] that could be additionally dried under vacuum at 80 °C. After drying we recovered 10.5 g of ionic liquid that could be used in additional reactions.